cuprate or Michael additions, *etc.*) of a variety of saturated and functionally substituted acyl groups.[7]

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Stereospecific Aliphatic Hydroxylation by an Iron-Based Oxidant

Sir:

There has been much recent interest in the nature of iron species responsible for oxidation of organic substrates by mixed function oxidases as well as the relation of these intermediates to a number of nonenzymatic model systems.[1] While these studies have demonstrated the ability of nonenzymatic oxidants to effect aromatic hydroxylation and olefin epoxidation, there has been as yet no demonstration that a simple iron-derived reagent could mimic the stereospecific aliphatic hydroxylation observed in biological systems.[2] We report here an examination of the ferrous ion–hydrogen peroxide oxidation of cyclohexanol which has now revealed a pronounced regioselectivity and stereoselectivity for hydroxylation to cyclohexanediols. We interpret these results as evidence for the interception of a metal-bound oxidant, not free hydroxyl radical, which is subject to strong substituent-derived directive effects and may be a prototype of the reactive oxy–iron intermediates of the mixed function oxidases.

In a typical experiment, 30% hydrogen peroxide in acetonitrile was added to an acetonitrile solution of cyclohexanol containing perchloric acid and ferrous perchlorate.[1e] The entire reaction mixture was acetylated with acetic anhydride–pyridine for analysis of products by glpc. The only significant products were cyclohexanone and the diacetates of all six possible cyclohexanediols.[3]

Analysis of the diol products (Table I) reveals several startling features of this reaction. First, it is apparent that C-3 of cyclohexanol is intrinsically more reactive than either C-2 or C-4 when ferrous ion is used, accounting for more than 70% of the hydroxylation in the less aqueous medium. When cuprous ion is substituted for iron this specificity is lost and the most reactive position becomes C-4 with reactivity decreasing at positions closer to the electronegative substituent. This latter result is more in accord with predictions based on the operation of a polar effect,[4] even if the proportion of 1,2-diol is anomalously low. The specificity for C-3 attack is favored by removal of water from the system but temperature seems to have little effect between 25 and −18°.

Table I. Product Distribution for Cyclohexanol Hydroxylation

Isomer	%[a] a	b	c[b]	d
Cis-1,2	5.2	4.8	6.7	0.25
Trans-1,2	14.3	8.8	12.3	4.0
Cis-1,3	37.0	70.1	71.9	30.35
Trans-1,3	15.0	5.1	2.5	26.4
Cis-1,4	17.5	3.7	3.8	17.8
Trans-1,4	11.0	7.1	2.9	21.2
Diol yield (%)	36	25	66	29
Conversion (%)	17	12	6	7

[a] Results for adding 30% H_2O_2 (3.68 equiv) to a solution of cyclohexanol (0.19 *M*) and perchloric acid (0.1 *M*) in: (a) 50% CH_3CN–H_2O containing $Fe(ClO_4)_2$ (0.19 *M*) at 25°; (b) 90% CH_3CN–H_2O containing $Fe(ClO_4)_2$ (0.19 *M*) at 25°; (c) 90% CH_3CN–H_2O containing $Fe(ClO_4)_2$ (0.19 *M*) at −18°; (d) 50% CH_3CN–H_2O containing $Cu(ClO_4)_2$ (0.19 *M*) at 25°. [b] Relative rates of hydroxylation (per hydrogen): C-1, 150; C-2, 13; C-3, 106; C-4, 10; cyclohexane, 1.00.

The cis–trans ratios of the products are also revealing. In 50% aqueous acetonitrile the amounts of cis and trans products are comparable; however, in the less aqueous medium the ratio of cis- to trans-1,3-diol increases dramatically to 28.8:1. Thus, *the major diol product is formed with greater than 96% stereoselectivity* at −18°.

In competition experiments with toluene we find that k(cyclohexane)/k(toluene) = 0.27 on a per-hydrogen basis. This is not in accord with results obtained for chlorine atoms or *tert*-butoxy radicals for which k-(cyclohexane)/k(toluene) is reported to be 2.35[5] and 1.50,[6] respectively. Another contrast is observed upon comparison of the relative rates of reaction of cyclohexane and cyclohexanol (Table I). First, the much greater reactivity of cyclohexanol is not in accord with the expected polar effect on an electrophilic free radical[4] (for example, k(cyclohexane)/k(cyclohexanol) = 1.63 for *tert*-butoxy radicals).[7] More interesting, however, is the comparison of the reactivity of C-3 in cyclohexanol to cyclohexane, *the former being 106 times more reactive.*

While these results appear inconsistent with a mechanism involving free hydroxyl radical,[1e,8] they are in accord with a scheme mediated instead by an iron species[9] (Scheme I). Chelation of this intermediate by cyclohexanol and hydrogen abstraction through a cyclic transition state reminiscent of the Barton reaction[10] would explain the high reactivity of the alcohol.

(1) (a) H. J. Fenton, *Proc. Chem. Soc., London*, 9, 113 (1893); (b) W. A. Waters, "The Chemistry of Free Radical," Oxford University Press, New York, N. Y., 1948, p 247; (c) S. Undenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie, *J. Biol. Chem.*, 208, 731 (1954); (d) G. A. Hamilton, J. W. Hanifin, and J. P. Friedman, *J. Amer. Chem. Soc.*, **88**, 5269 (1966); (e) C. Walling and S. Kato, *ibid.*, **93**, 4275 (1971); (f) K. B. Sharpless and T. C. Flood, *ibid.*, **93**, 2318 (1971); (g) K. B. Sharpless and R. C. Michaelson, *ibid.*, **95**, 6137 (1973); (h) H. S. Mason, *Annu. Rev. Biochem.*, **34**, 595 (1965).

(2) Stereospecific hydroxylation by chromium salts has been observed, K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1965, p 109 ff.

(3) These products accounted for all the cyclohexanol consumed. Appropriate controls were performed to establish the integrity of the products under the reaction conditions and the quantitative viability of the work-up and assay. Specifically absent were cyclohexenyl acetates, cyclohexane triacetates, and 4,4′-diacetoxydicyclohexyls.

(4) (a) C. Walling and B. Miller, *J. Amer. Chem. Soc.*, 79, 4181 (1957); (b) G. A. Russell, *J. Org. Chem.*, **23**, 1407 (1958).

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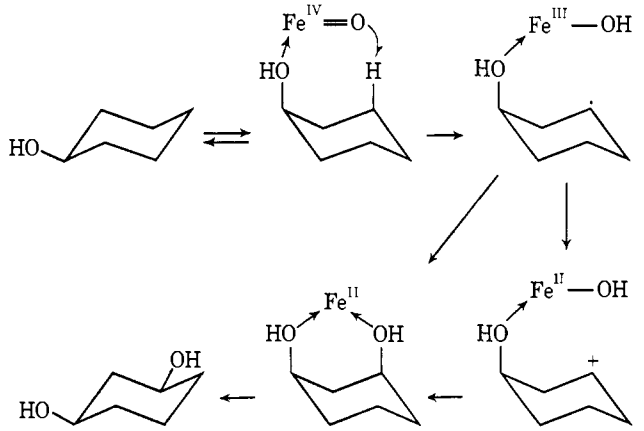
(10) (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechot, *J. Amer. Chem. Soc.*, **82**, 2640 (1960); (b) *ibid.*, **83**, 4076 (1961).

Scheme I



If bond lengths and angles are appropriate, collinearity of the C···H···O moiety, a requisite in other free radical hydrogen abstractions,[11] may be more easily obtained by attack at C-3 although it is not apparent from models that a trans-diequitorial attack at C-2 should be disfavored strictly on this geometrical basis. Indeed, there appears to be a small but significant increase in the proportion of 1,2-diol when iron salts are used. The near-exclusive formation of *cis*-1,3-cyclohexanediol can be economically explained by directed oxidation of the incipient alkyl radical by the proximate iron(III) by either an electron transfer or ligand transfer process.[12] Competition for the intermediate cyclohexyl carbonium ion by solvent can account for the loss of stereoselectivity upon addition of water.

The operation of this mechanism requires a stereospecific removal of the C-3 hydrogen cis to the hydroxyl group. That cis-hydrogen abstraction does indeed predominate was determined by examination of hydroxylation products of *trans*-3-*trans*-5-cyclohexanol-d_2 (**1**).[13] The deuterium content of **1** was found to be 2.0 from its mass spectrum while integration of the Eu(fod)$_3$-shifted pmr spectrum[14] indicated that 88.5% of the deuterium content was trans at C-3 and C-5, the remainder being cis.

Oxidation of **1** again afforded *cis*-1,3-cyclohexanediol as the major hydroxylation product, the mass spectrum of which indicated a 3:1 ratio of dideuterated to monodeuterated diol.[15]

While it is clear that much of the deuterium at C-3 has been retained in this oxidation, an accurate determination of the stereoselectivity for hydrogen abstraction requires the measurement of the hydrogen isotope effect for this reaction. This value was determined by a competitive oxidation of cyclohexane and cyclohexane-d_{12} which leads to k_H/k_D = 1.26 for cyclohexane → cyclohexanol and k_H/k_D = 1.75 for cyclohexanol → cyclohexanone.

The hydrogen isotope effect for oxidation of cyclohexanol to cyclohexanone observed here is in close accord with the value determined by Walling[1e] for isopropyl alcohol in an aqueous medium with Fenton's reagent, suggesting a similar mechanism. The hydroxylation of cyclohexane, however, shows an anomalously small hydrogen isotope effect, and we interpret this low value as an indication of a change in the nature of the oxidant from that in water solution.

With the value of the hydrogen isotope effect, k_H/k_D = 1.26, and the known stereochemical integrity of **1**, one must conclude that hydrogen abstraction from C-3 occurs cis to the hydroxyl group of cyclohexanol 80% of the time. Thus, in accord with the proposed mechanism (Scheme I), the conversion of cyclohexanol to *cis*-1,3-cyclohexane diol occurs with *net retention* at C-3.[16] Further elaboration of the nature of this iron-derived oxidant and its relationship to intermediates involved in enzymatic hydroxylation are currently under way.

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(16) While oxidation with net retention can also be accommodated by an "oxene" mechanism involving direct insertion, we have observed stereoselective oxidation of 3-hydroxycyclohexyl radicals generated independently in the presence of ferric ions. J. T. Groves and M. Van Der Puy, unpublished results.

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(12) J. K. Kochi, A. Bemis, and C. L. Jenkins, *J. Amer. Chem. Soc.*, **90**, 4616 (1968), and references to earlier work therein.
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(14) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1524 (1971).
(15) (a) *cis*-1,3-Cyclohexanediol, *m/e* (relative intensity) 117 (7.2), 116 (100.0), 115 (4.3), 114 (5.3); *cis*-1,3-cyclohexanediol-d_n, *m/e* (relative intensity) 119 (18.0), 118 (100.0), 117 (36.9), 116 (10.7). (b) Similar oxidation of cyclohexanol deuterated at C-4 afforded *cis*-1,3-cyclohexanediol with *complete* retention of the label.

Influence of Solvent on the Mobility of Molecules Covalently Bound to Polystyrene Matrices

Sir:

Despite the growing body of knowledge relating to chemical reactions occurring on polymer supports, there still exists only a primitive level of understanding of the physical and chemical nature of "immobilized" substrates and the role which the solvent plays in these heterogeneous systems.[1]

We wish to report the use of the spin-labeling technique in examining the mobility of a nitroxide bound to cross-linked polystyrene in the solvent-swelled state.[2] Our results establish (1) the choice of swelling solvent has a substantial influence on the physical nature of the resin-bound nitroxide and (2) the dominant role of solvent is to define the degree of swelling of the polymer lattice.

The nitroxide 2,2,6,6-tetramethyl-4-piperidinol-1-oxyl (**1**) was covalently attached to polystyrene by reaction with 2% cross-linked chloromethylated polystyrene (**2**)

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